Remarks

In response to the final rejection of October 7, 2003, Applicants filed a response, to which the Examiner responded with an Advisory Action, in which all rejections were maintained. The Examiner's comments in the Advisory Action regarding the maintenance of the rejections (in particular, the rejections under Section 102(b) over Boyce et al. and Dower et al.) seem to indicate that if the limitation "the sequence or structure of the compound is determined by in-situ optical interrogation," was added to the claims, all the rejections would be withdrawn. Applicants have added the term "to provide the chemical identity" rather than reciting "sequence or structure." The term "identity" is defined as: "The collective aspect of the set of characteristics by which a thing is definitively recognizable or known." *See* Online American Heritage dictionary at http://education.yahoo.com/ reference/dictionary/entries/02/i0020200.htmas. The term "chemical identity" was selected by Applicants as it appears expressly several times in the specification, as follows:

> At the start of the Detailed Description (page 9, lines 16 to 21) it states:
>
> The color coding strategy of the present invention provides a method to place a set of fluorophores - or, more generally, chromophores - on each bead so as to uniquely encode the *chemical identity* of the compound on that bead. Specifically, during each coupling step in the course of DCR combinatorial synthesis, one or more fluorophores are attached to each bead. Decoding is based on the determination of relative abundances of fluorophores on a bead of interest by in-situ optical interrogation. [emphasis added]
>
> In the Summary of the Invention section (page 8, lines4 to 7) it states:
>
> The *identity of the compound anchored to any specific bead is determined in-situ by optically probing individual beads* to read the color code, as described herein. This ensures the identification of bead-anchored chemical compounds without the need for physical separation and without the need for off-line chemical analysis. [emphasis added]

And in the Background Section (page 2, lines 27 to 32), it states:

> 1.2 - Encoded One Bead/One Component Chemical Libraries One approach to overcoming the serious limitations of standard one bead/one compound chemical libraries is to *encode chemical compound identities*. This facilitates the identification of compounds not amenable to direct determination by micro-sequencing or mass spectrometry. [emphasis added]

Applicants also re-ordered claim 129 by moving the phrase "in-situ optical interrogation of the tag(s)" to the front of subparagraph(g), for reasons of syntax.

Regarding maintenance of the 102(b) rejection over Still et al., the Examiner has stated that:

> Applicant's response does not overcome the rejection of the claims over Still et al. for the following reasons. Applicants argue that the reference method of decoding step is not carried out without isolating the solid support of interest from other solid supports as in the instant claims. Applicant's arguments have been fully considered and are not persuasive, since the reference teaches that the fluorescent beads with the compounds of interest are identified manually which would read on the "identifying the compound by in-situ optical interrogation" of the instant claims.

The Examiner's comments above are not responsive to the issue raised by Applicants. Applicants were contending that the claims require that "the decoding step is carried out without isolating the solid support" (set forth in claim 129), and this step was not disclosed in Still et al. In response, the Examiner does not address the lack of this element, but states that Still et al. "read on the 'identifying the compound by in-situ optical interrogation...'" Moreover, Applicants review of Still et al. (as set forth on pages 6 and 7 of their prior response at) demonstrates that Still et al. do not disclose that: "the decoding step is carried out without isolating the solid support," as required in claim 129. If the Examiner disagrees, she is requested to indicate where in Still et al. this element appears, as this was not done in the Advisory Action. Absent such a showing, the rejection over Still et al. must be withdrawn, because a rejection for anticipation is

only proper if "each and every element set forth in the claim [is] disclosed in a single reference." MPEP 2131.

Also as noted in the prior response, Still et al. also do not disclose decoding "without detaching any of the tags from the solid support of interest," as set forth in claim 129, and in fact teach the opposite, *i.e.*,: "[e]ach selected fluorescent bead is subjected to a means for releasing at least some of the tags from the bead." *See* Col. 17, lines 16-18 of Still et al. The Examiner did not address the lack of such element in Still et al. in the Advisory Action. If the Examiner feels that such element is present in Still et al., she is requested to indicate where in Still et al. it appears. Absent such a showing (irrespective of the presence of other disputed elements), the rejection over Still et al. must be withdrawn, because a rejection for anticipation is only proper if "each and every element set forth in the claim [is] disclosed in a single reference." MPEP 2131.

Regarding the rejection under Section 103 over Dower et al. and Metzeker et al., the Examiner has reiterated in the Advisory Action that:

> One cannot show nonboviousness by attacking references individually where the rejections are based on combinations of references. [*citing In re Keller* and *In re Merck & Co.*] The rejection is based on the combined teachings of Dower et al. and Metzeker et al.

Applicants did, in fact, base their prior response to this rejection on the "combined teachings of Dower et al. and Metzeker et al." Applicants demonstrate below that even if these references are combined, a *prima facie* case of obviousness is not established.

MPEP Section 2143 provides:

> To establish a *prima facie* case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must

> be a reasonable expectation of success. *Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations.* [emphasis added]

The combined teachings of Dower et al. and Metzker et al. do not "teach or suggest all the claim limitations," because neither of them, together or separately, teach or suggest that the "decoding step is carried out without isolating the solid support of interest from other solid supports ..." as required in claim 129. Metzker et al. do not in any way relate to use of solid supports or to "decoding the code composed of one or more tag(s) by in-situ optical interrogation of the tag(s) to provide the chemical *identity of the compound associated with the code*," but only to identification *of classes of polynucleotides* in a gel using certain dyes described therein (see further explanation of Metzker et al. below). The only mention of decoding of identifier tags in Dower et al. relates to the decoding of oligonucleotide sequence tags. Moreover, Dower et al. provide that the identifier tags are decoded by sequencing (page 4, lines 21 to 33). Decoding by sequencing normally involves *isolation* "of the solid support of interest from other solid supports ..."

Although fluorescent tags are mentioned in Dower et al., their decoding is not described. Dower et al. provide that beads to be decoded are always isolated. *See, e.g.*, page 30, lines 5 to 25

> The techniques for *selection of individual beads displaying ligands on their surface* are analogous to FACS methods for cloning mammalian cells ... . After washing away unbound or non-specifically bound receptors, one can then use FACS to sort the beads and to *identify and isolate physically individual beads* showing high fluorescence....
> Alternatively, affinity adsorption techniques can be employed in conjunction with the libraries of the invention. [Dower et al. then describe an affinity adsorption procedure, where the procedure includes the step that:] Finally, individual beads are *physically separated* ..." (emphasis added))

Accordingly, even if Dower et al. and Metzeker et al. are combined, they do not "teach or suggest" the claim limitation that: "decoding step is carried out without isolating the solid support of interest from other solid supports ..." and, accordingly, a *prima facie* case of obviousness has not been established by the combination of these references.

The Examiner also states that

> Applicants argue that Dower et al.'s teachings are teaching away from the claimed invention. Applicant's arguments have been considered and are not persuasive, since Dower et al. teach the use of fluorescent tags, the tags other than the oligonucleotide tags as in applicant's arguments.

In fact, Applicants noted in their prior response, page 9 and footnote 2, that Dower et al. disclosed in the Summary of the Invention that: "the identifier tag may be a set of light-addressable compounds, such as fluorescent and phosphorescent compounds that can be pohotobleached ..." Although fluorescent tags are mentioned here, their decoding (and their encoding) is not described. Applicants' point in their prior response was that Dower et al. do not mention anywhere that, with respect to any type of identifier tags (including fluorescent compounds or oligonucleotides or any other compounds), the "decoding step is carried out without isolating the solid support of interest from other solid supports ..." as required in claim 129. . The only mention of decoding of any identifier tags in Dower et al. relates to the decoding of oligonucleotide tags. Dower et al. provide that beads to be decoded are always isolated (page 30, lines 5-25, *supra*). Moreover, Dower et al. state that identifier tags are decoded by sequencing (page 4, lines 21 to 33) which normally involves *isolation* "of the solid support of interest from other solid supports ..." Because isolation of the solid support is the only means taught in Dower et al. for decoding, this

suggests that the solid supports must be isolated irrespective of whether one is decoding oligonucleotide tags or fluorescent tags.

Metzker et al. only describe the use of modified versions of a new class of dyes, *i.e.*, BODIPY.RTM. fluorophores, for DNA sequencing by the chain termination method of DNA sequencing. As set forth in their claim 1, Metzker et al. relates to a method for distinguishing among four types of polynucleotides, each distinguished by having different 3'-terminal dideoxynucleotides, based on attaching one of four different fluorophores to each of the four different types of polynucleotides and running them in an electrophoresis gel, or by attaching the same fluorophore to all four different types of polynucleotides, but separating each type of polynucleotide by running it in a separate electrophoretic lane from the others. Metzker et al. also describe use of these dyes in internal labelling of polynucleotides by enzymatic incorporation of fluorescently-labeled ribonucleotides or deoxyribonucleotides.

Metzker et al. do not in any way suggest or motivate one to make the invention, as these dyes and methods are not used for "decoding the code composed of one or more tag(s) by in-situ optical interrogation of the tag(s) to provide the chemical identity of the compound associated with the code," as in claim 129. Metzker et al.'s method only allows determination of *classes of polynucleotides* (*not identities* of polynucleotides) which have the same 3'-terminal dideoxynucleotides (see claims 1-6 of Metzker et al.), or *classes* which contain the same ribonucleotides (claim 7 of Metzker et al.) or *classes* which contain the same deoxynucleotides (claim 12 of Metzker et al.). Metzker et al. do not, therefore, affect the teaching away from the invention in Dower et al. Accordingly, there is no motivation to modify Dower et al. to provide decoding (and the *identities* of

compounds) *without* isolation of the solid supports, and for this further reason, there is no *prima facie* case of obviousness. *See* MPEP 2143.

For the foregoing reasons, Applicants assert that all rejections should be withdrawn and a notice of allowance should be issued.

Respectfully submitted,

Dated: 11/20/03 By: _____

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Applicants) hereby petitions for any extension of time or for any other grounds needed to make this submission timely and proper. The Commissioner is hereby authorized to charge any fees due in connection with this submission and not otherwise covered by payment included herewith, or to credit any overpayment, to Deposit Account No. 502088.

I hereby certify that, on the date indicated below, this correspondence was sent by fax to the Commissioner for Patents, at (703) 872-9306.

By: Suzanne K Klein Date: 11-20-03